REMARKS

In response to the Office Action of October 18, 2002, claims13 and 23 are hereby amended and claim 22 is canceled. Claims 13, 15 and 16 were rejected under 35 U.S.C. § 102(b) as being anticipated by Southard *et al.*, U.S. Pat. No. 5,013,553 and claims 13, 15, 16, 19 and 22, 23 and 26 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Southard *et al.*, U.S. Pat. No. 5,013,553 in view of Mehltretter *et al.*, U.S. Pat. No. 2,715,627. Each of these rejections is discussed below.

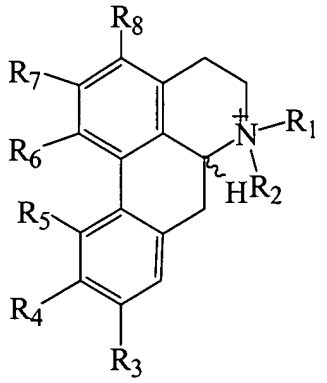
Rejection under 35 U.S.C. § 102(b)

The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); Alco Standard Corp. v. Tennessee Valley Auth., 1 USPQ2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991) (citations omitted). The Court of Appeals also provides, however, that if a prior art reference does not expressly set forth a particular element of the claim, that reference may still anticipate if that element is inherent in its disclosure. In re Robertson, 49 USPQ2d 1949,1950 (Fed. Cir. 1999). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." In re Robertson, 49 USPQ2d 1949,1950 (Fed. Cir. 1999) (emphasis added). Inherency may not be established by probabilities or possibilities, thus the mere fact that a certain thing may result may result from a given set of circumstances is not sufficient to establish inherency. In re Robertson, 49 USPQ2d 1949,1951 (Fed. Cir. 1999).

The Examiner has rejected claims 13, 15 and 16 under 35 U.S.C. § 102(b) as being anticipated by Southard *et al.*, U.S. Pat. No. 5,013,553 for the reasons stated in the Office Action mailed May 21, 2002. Briefly, the Examiner reasons that these claims are drawn to a method for isolation and purification of an isoquinoline alkaloid via extraction of a ground biomass of a

plant with a solvent, neutralization and further concentration. These claims are further drawn to purification of the extract by a chromatographic method, wherein the plant is selected from a group of specific plant families and genus. The Examiner concludes that the method steps as outlined in claims 13, 15 and 16 are disclosed by Southard *et al.* Regarding Applicant's contention that the method of this invention is different because it extracts aporphine alkaloids, the Examiner provides that if there is a difference, the differences do not appear in the claims. The Examiner further provides that "since the method are the same, the extract disclosed by Southard *et al.* must have inherently contained aporphine alkaloids."

In response to this rejection, independent claim 13 has been amended to include the subject matter of claim 22, which was not rejected as being anticipated by Southard *et al.* and claim 22 has been canceled. As amended, claim 13 is now drawn to a method for the isolation and purification of aporphine alkaloids having the following structure:



Southard *et al.* do not disclose or suggest that their method can be extended to this group of compounds. As noted above, anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. The present invention, as amended, describes and claims a method for the isolation and purification of a specific group of aporphine alkaloids. As described in detail below, this group aporphine alkaloids have a different structure and as a result different physical and chemical properties than benzophenanthridine alkaloids. Applicant maintains that, as amended, the claims are not anticipated by the Southard *et al.* reference which teaches a method for extracting and isolating benzophenanthridine alkaloids. Applicant also maintains that due to the differing structure and properties of these two different classes of alkaloids that the Examiner cannot conclude that the method of Southard *et al.* could necessarily

be used to purify the aporphine alkaloids as set forth in claim 13, as amended, and further that this fact would have been recognized by persons of ordinary skill in the art. Applicant maintains that the claims, as amended, are not anticipated by the Southard *et al.* reference and therefore respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

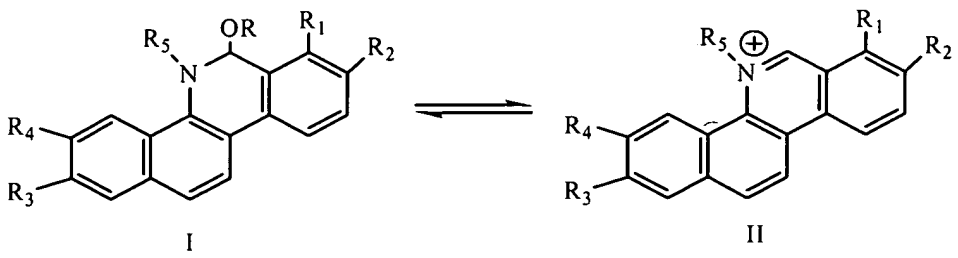
The Examiner has rejected claims 13, 15, 16, 19, 22, 23 and 26 under 35 U.S.C. § 103(a), as being unpatentable over Southard *et al.* U.S. Pat. No. 5,013,553 in view of Mehltretter *et al.*, U.S. Pat. No. 2,715,627.

The Examiner bears the burden of establishing a prima facie case of obviousness. In determining obviousness, one must focus on Applicant's invention as a whole. Symbol Technologies Inc. v. Opticon Inc., 19 USPQ2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success. . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicant asserts that the cited references do not disclose or suggest the present invention and therefore, do not render the present invention obvious.

As noted above, Southard *et al.* describe a method for isolating benzophenanthridine alkaloids, which have the following structures:

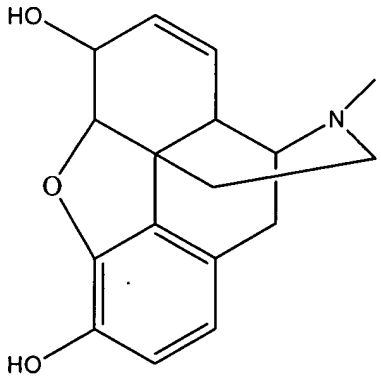


I II

benzophenanthridine alkaloids

from plants via extraction with a mineral acid/alcohol solvent, precipitation with a base and dissolution in water (neutralization), precipitation and drying (concentrating) and further purification by silica gel column chromatography. These compounds exist in the form of the iminium ion (structure II) only at very low pH. As noted above, Southard *et al.* do not disclose or suggest that their method can be extended to other alkaloids.

Mehltretter *et al.* disclose and claim a method for extracting opium alkaloids, specifically morphine and associated alkaloids from poppy. (Mehltretter *et al.*, col. 1, lines 21-25). The method described by Mehltretter *et al.* involves extraction with mineral acids, neutralization and evaporation. Mehltretter *et al.* also provide that the extract may be optionally purified by ion exchange chromatography (col. 2, lines 44-65), however, no examples of this technique are provided in the Specification. Morphine, is a phenanthrene alkaloid having the following structure:



Morphine

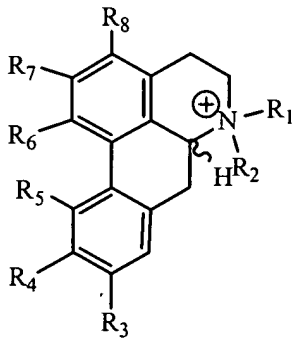
Mehltretter *et al.* do not disclose or suggest that their method can be extended to other alkaloids.

The Examiner has rejected claims 13, 15, 16, 19, 22 and 23 for the reasons set forth in the Office Action mailed May 21, 2002. Briefly, the Examiner reasons that although these references do not state whether the methods described can be applied to other alkaloids, such as the aporphine alkaloids magnoflorine or laurifoline,"one of ordinary skill in the art would have had a reasonable expectation that alkaloids, having similar isoquinoline structures would have been extracted via the method proposed by Southard et al. (US 5013,553)." The Examiner further reasons that "[o]ne of ordinary skill in the art would have recognized that an extraction

with an alcohol and/or acid would have produced a product containing aporphine alkaloids since alkaloids would have had similar polarities due to their phenolic rings." Additionally, the Examiner reasons that as evidenced by Mehltretter *et al.*, "alkaloids such as morphine, a phenanthrene alkaloid, is extracted with mineral acids, neutralization, evaporation and optional purification via column chromatography. (Col. 2, lines 44-65)." From this the Examiner concludes that "although the structure of phenanthrene alkaloids are different, one of ordinary skill in the art would have reasonably appraised that the alkaloids of a plant (isoquinoline, aporphine, benzophenanthridine, etc.) could have been extracted with an acid or an alcohol to obtain a crude alkaloid product."

In response to Applicant's argument that aporphine alkaloids are structurally different, resulting in different physical properties, the Examiner provides that this argument has not been clearly substantiated by Applicant. The Examiner concludes therefore, that "although the structure of aporphine alkaloids differ with respect to benzophenanthridine alkaloids or phenanthrene alkaloids, the properties of the solubilities of the compounds would be similar due the similarities of phenolic groups . . . ."

In response to this rejection, the present invention has been amended to clarify that the present invention is drawn to a method for the isolation and purification of a specific group of aporphine alkaloids, which have the following structure:



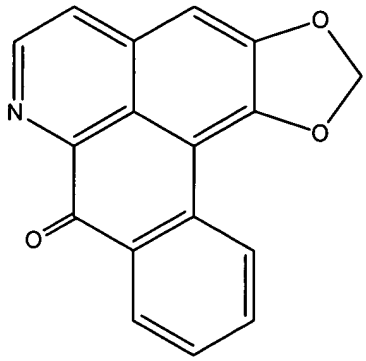
aporphine alkaloids

As amended, the present invention is drawn to a method for the isolation and purification of a specific class of aporphine alkaloids that contain a positively charged quaternary amine group. As explained in detail below, it is this positively charged group which differentiates the physical

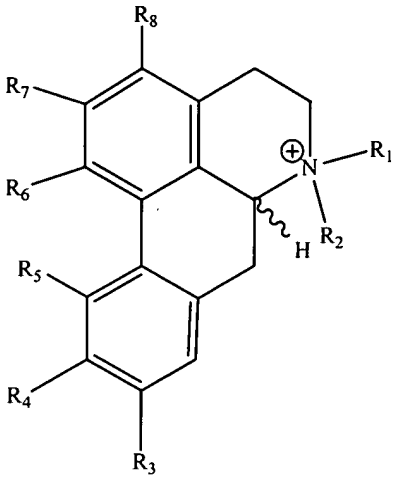
properties of the claimed compounds from the compounds isolated in the art relied upon by the Examiner. Each of the points raised by the Examiner is addressed below in light of this amendment to the claims.

With respect to Applicant's contention that aporphine alkaloids will not elute from a silica gel column, the Examiner provides that in the instant Specification, the aporphine alkaloid Liriodenine is purified by silica gel column chromatography. The Examiner concludes from this that Applicant's statements with regard to column chromatography are contradictory and therefore not convincing. The Examiner further provides that "silica gel is a type of 'size exclusion' chromatography, although it does contain constituents on the gel which also provide for some 'adherence' effect."

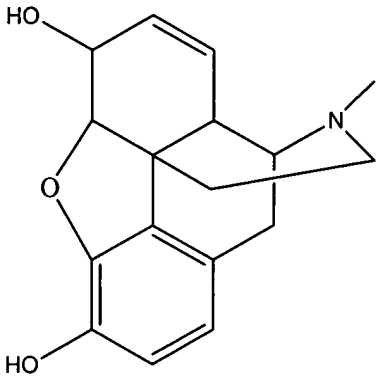
As noted by the Examiner Liriodenine, which is not a positively charged quaternary amine, is an aporphine type alkaloid that can be purified by silica gel column chromatography. Liriodenine type aporphine alkaloids, however, do not fall within the scope of the currently claimed invention. As illustrated by the structures below, Liriodenine does not contain a positively charged quaternary amine group, nor does it contain phenolic hydroxyl group(s) as do the claimed aporphine alkaloids, such as magnoflorine and laurifoline. Therefore, Liriodenine, being a neutral compound, would be expected and known in the art to have totally different physical properties, including the ability to be purified using silica gel absorption chromatography, whereas as explained in more detail below, the positively charged compounds of this invention would not be expected to elute from a normal phase silica gel column.



Liriodenine



claimed aporphine alkaloids



Morphine

Silica gel has been widely utilized in chromatography technology and the various methods of silica gel chromatography are well known to those of skill in the art. As noted by the Examiner, based upon the pore size and the functional groups on the surface of the particles, silica gel can be utilized for absorption (normal phase), reverse phase and size exclusion phase chromatography. Silica gel having a pore size of 100 Å or less and having a fully hydroxylated surface is utilized for absorption chromatography. Organic solvents and combinations thereof are used to elute compounds from the column. The retention of compounds on the column is based on hydrogen bonds, dipole moment and other hydrophilic interactions, with low polarity compounds eluting first. It is well known in the art that adsorption phase silica gel chromatography cannot be used to purify charged compounds because irreversible absorption and the difficulty involved in eluting these compounds from the column will lead to very low recovery of the compound of interest.

Silica gel having a pore size of 100 Å or less and having a surface derivatized with C18, C8, C4, as well as, other functional groups is used for reverse phase column chromatography. A combination of water and high polarity organic solvents, such as, methanol and acetonitrile are used to elute compounds from reverse phase columns. The retention of compounds on the

column is based on Van der Waals' forces and other hydrophobic interactions, with high polarity compounds eluting first.

Silica gel having a pore size >100 Å and having a surface modified by reactions with organic substituents to reduce adsorption is utilized for size exclusive column chromatography. Water, buffered solutions, high polarity organic solvents and combinations thereof are used to elute compounds via size exclusive chromatography. The retention of compounds on the column is based on the size and molecular weight of the compounds, with compounds having the largest size eluting first.

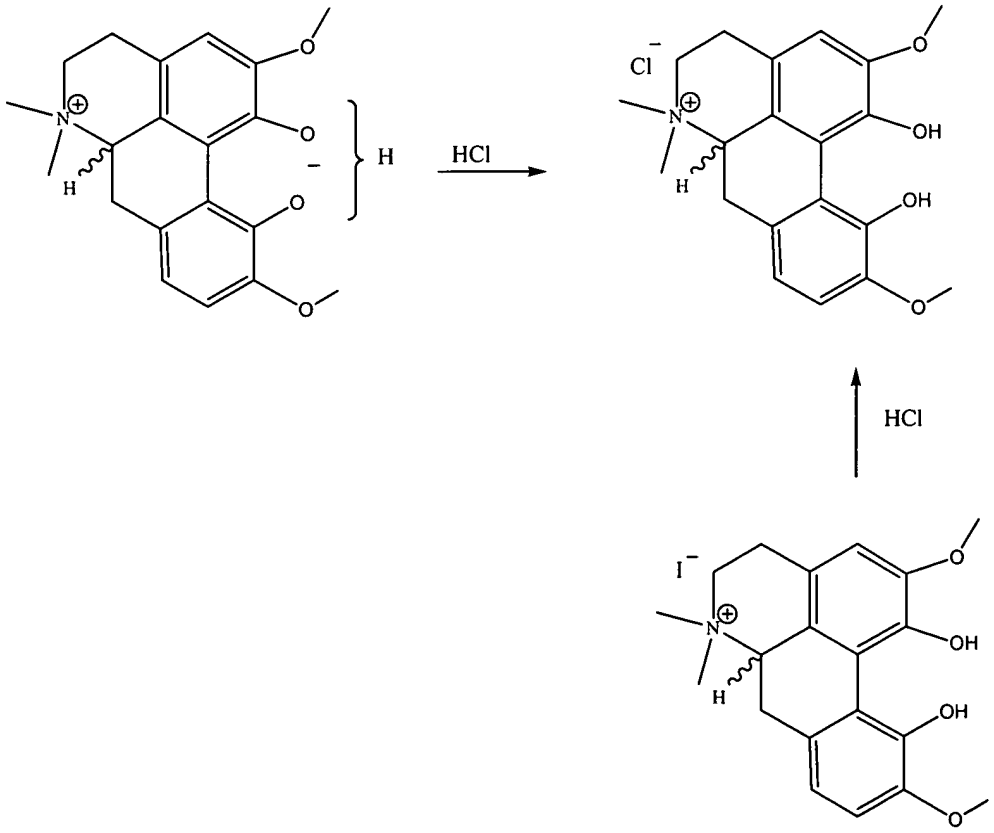
Southard *et al.* does not disclose the type of column chromatography being employed for purification of the disclosed benzophenanthridine alkaloids. However, based upon the solvents utilized for the separation, i.e. ethyl acetate and methanol, it can be concluded that the silica gel was used for a normal phase, adsorption column chromatography. As provided above, the positively charged compounds of this invention cannot be purified by normal phase adsorption chromatography. The separations of the claimed aporphine type alkaloids using reverse phase, ion exchange, and size exclusion column chromatographic methods have totally different mechanism of actions with different packing materials, solvent systems and elution profiles. Although Mehltretter *et al.* provide that phenanthrene alkaloids can be purified by ion exchange chromatography, no examples are provided. Furthermore, it does not necessarily follow that the positively charged aporphine alkaloids can also be purified using this method. Mehltretter *et al.* do not describe or suggest that their method can be extended to other types of alkaloids.

The Examiner also concludes that although the structure of these three classes of alkaloids are different, one of ordinary skill in the art would have reasonably appraised that the alkaloids of a plant (isoquinoline, aporphine, benzophenanthridine, etc.) could have been extracted with an acid or an alcohol to obtain a crude alkaloid product. Applicant maintains, however, that this is <u>not</u> the case. For example, although morphine does contain phenolic hydroxyl groups, as noted by the Examiner, it is an alkaloid with a tertiary amine that possesses no charge in the molecule and therefore, the polarity of morphine is moderate. The claims, as amended, are drawn to the isolation and purification of aporphine alkaloids containing a positively charged quaternary amine. These positively charged alkaloids have a much higher

polarity and greater water solubility than morphine type alkaloids. One of the best indicators of the solubility of a compound is the partition coefficient for that compound (calculated log P), which is a measure of the relative hydrophobicity/hydrophilicity of a compound. The partition coefficient represents the relative distribution of a compound between a non-miscible organic solvent and water, for example octanol and water. Compounds having values of log P greater than 1 are classified as lipophilic compounds, whereas those having negative log P values are classified as hydrophilic compounds. The calculated log P value for morphine is 0.72, which means that morphine is distributed 5.25 times more in octanol than in water. The calculated log P value for magnoflorine is -0.32, which means that magnoflorine is distributed 2.1 times more in water than in octanol. Based on log P values, morphine is approximately 10 times more hydrophobic than magnoflorine. Thus, contrary to the Examiners' contention, the properties of these compounds, such as solubility are not at all similar. Based upon this information, it would be virtually impossible to use the solubility and extraction/purification protocol of morphine to predict the extraction/purification protocol for the currently claimed aporphine alkaloids. (For the Examiners' ease of reference Applicant has attached as Appendix A, the calculated partition coefficients for morphine and magnoflorine. Applicant has also attached a sheet indicating that the Log P for the benzophenanthridine alkaloid chelerythrine is 0.11, which means that chelerythrine is 1.29 times more soluble in n-octanol than in water. Chelerythrine is therefore 2.7 times less soluble in water than Magnoflorine.)

The Examiner has rejected new claim 26, under 35 U.S.C. § 103(a), as being unpatentable over Southard *et al.* U.S. Pat. No. 5,013,553 in view of Mehltretter *et al.*, U.S. Pat. No. 2,715,627. The Examiner provides that Southard *et al.* teach that an extract was dissoluted in water, but did not state wherein the extract was neutralized to a pH between 4.5 and 7.0. The Examiner reasons however that "because the basic extract was dissoluted in water, the ordinary artisan would have recognized that the pH of the solution after dissolution would have been approximately 7 [before] prior to precipitation with acid." Thus, the Examiner concludes that one of ordinary skill in the art would have been motivated to have neutralized the extract to about a pH of 7. Applicant respectfully traverses this rejection.

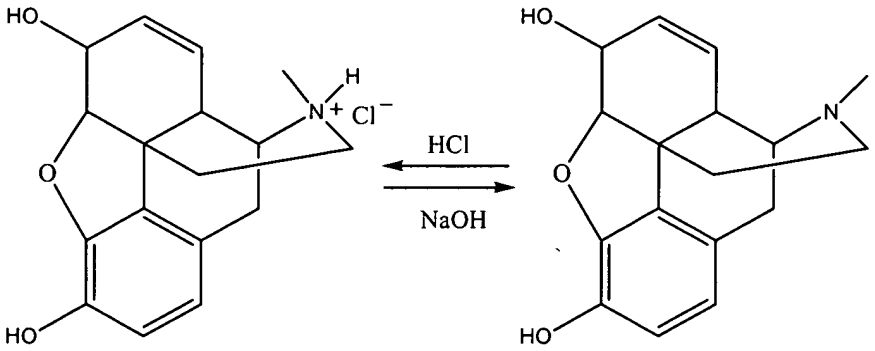
The purpose of pH adjustment to 4.5-7.0 in current invention is completely different from the precipitations with acid and base taught by Southard *et al.* The claimed aporphine alkaloids are quaternary amines and exist in plants as different inorganic and organic salts and/or inter-dissociated compounds. (See Ishii *et al.* (1994) Chem. Pharm. Bull. 42:108-111 and Hoard and Elakovich (1996) Phytochemistry 43:1129-1133 (Appendix B)). The different forms of the alkaloid salts or ion-pairs have different solubilities, as well as, other physical properties. Thus, the same alkaloid, existing in two different forms produces a split peak in a chromatographic separation. When the pH of the extract solution is adjusted with hydrogen chloride to a pH between 4.5 to 7.0, the purpose is not to precipitate the alkaloids, but rather to convert all of the aporphine alkaloids into their chloride salts, as illustrated below. In order to obtain reproducible separation results, it is important to maintain the structural consistency of the alkaloids.



Southard *et al.* teach a method for the purification of benzophenanthridine alkaloids utilizing the different solubility of the alkaloids at different pH conditions. With reference to the Specification (col. 4, lines 50 to 65), the benzophenanthridine alkaloids are extracted with a

mineral acid in an organic solvent. Under these conditions the alkaloid exists as the iminium ion (Form I, Figure 1A). The iminium ion is readily dissolved in alcohol and other moderately polar solvents. A base is then added to the solution, converting the iminium ion into the neutral compound (Form II, Figure 1B), which precipitates out of solution. This neutral compound can then be purified by normal phase silica gel absorption column chromatography as discussed above.

Mehltretter *et al.* teaches a method for extracting morphine from plants using an alcoholic solvent in the presence of a base. The amount of alkali used is that which will convert the alkaloids from their salt forms, as they occur in the plant, to their free organic base forms. (Specification, col. 2, lines 5-25). Mehltretter *et al.* also teaches a method for extracting morphine from plants using an acidic solvent, followed by precipitation with a base. (Specification, col. 2, lines 44-49). With reference to the scheme below, the basic solution was used to convert the alkaloid salt into the neutral alkaloid. As discussed above, in their neutral form, normal phase silica gel chromatography can be used to separate the compounds and organic solvent extraction can be performed.



In summary, the pH adjustment claimed in the current application is for consistency and reproducibility of the column chromatographic separation. Thus, the purpose and results of neutralization in the instant invention are totally different from the Southard *et al.* and Mehltretter *et al.* references. Therefore, Applicant maintains that the present invention is not rendered obvious by either of these references alone or in combination. Applicant has clearly demonstrated that the differences in chemical structure of these classes of alkaloids results in

them having different physical properties, solubility profiles and chromatographic behavior. Applicant maintains therefore that the claims, as amended, are not obvious over either of the cited references, alone or in combination.

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: February 18, 2003

Rosemary Kellogg, #39,726
Swanson & Bratschun, L.L.C.
1745 Shea Center Drive, Suite 330
Highlands Ranch, Colorado 80126
Telephone: (303) 268-0066
Facsimile: (303) 268-0065

cc: Qi Jia

S:\Client Folders\UniGen Pharmaceuticals\Uni15\Div\Uni.15 DIV OA 3.wpd